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THERMAL CHARACTERIZATION OF POLYETHYLENE GLYCOLS APPLIED IN THE PHARMACEUTICAL TECHNOLOGY USING DIFFERENTIAL SCANNING CALORIMETRY AND HOT STAGE MICROSCOPY

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Abstract

In the present study, the effect of the molecular weight and thermal treatments on commercial polyethylene glycols (PEG) samples used in the pharmaceutical processing technology, has been analyzed using DSC and HSM. The molecular weight of these polymers range from 1500 to 200000. Thermal investigations on the melting behavior of original PEG samples (as received from the manufacturer) showed only one single melting DSC endotherm effect before 373 K. This fact was associated to the presence of only one type of polymeric chain. Using standard conditions, PEG samples were solidified from the melt at 373 K, either by flash cooling (using liquid nitrogen and an ice bath) and by slow cooling, soaked and by slow cooling at room temperature. They were further studied by DSC. It was found that after cooling, PEG with molecular weight 1500 and 15000 showed DSC thermograms with a single endothermic peak. However, thermograms for PEG 4000 and 6000 produced a splitted melting endotherm. This fact was attributed to the presence of two types of chains, that are the folded and extended chains.

Ageing time influences also the shape of the DSC endothermal effects. It was concluded that the endotherms obtained after heating these PEG indicate that the thermal history determine the structure (extended or folded chain type forms) and the degree of crystallinity, as evidenced by changes in heat of fusion values, melting points and structures after crystallization. The relationships between melting enthalpies and melting points, as deduced from DSC diagrams, with molecular weight of the polymers are also presented.

Keywords: DSC, pharmaceutical technology, polymer

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Introduction

Polyethylene glycols (PEG) are a serie of water soluble synthetic polymers obtained by catalytic condensation of ethylene oxide and water. The general formula of these compounds corresponds to $HO–CH_2–CH_2–[O–CH_2–CH_2]_n–OH$ where *n* represents the average number of oxyethylene groups ($-OCH_2CH_2-$) or the degree of polymerization. PEG are semicrystalline polymers which, in the solid state, contain both amorphous and ordered crystalline regions in varying proportions depending upon the synthesis and their previous thermal history [1]. In the amorphous phase, the polymer chains have a random orientation. In the crystalline regions, the PEG molecules exist as a double parallel helix. The helices are arranged as plate-like structures known as lamellae. The chains within the lamellae may exist as extended or folded chains, depending on the molecular weight of the PEG. The folded chains are considered metastable as compared with the extended ones. The lamellae are, in turn, arranged in spherical structures with fine radiating branches, called spherulites [2]. The physical properties of these polymers are closely related to the thickness and distribution of lamellae, the crystallinity and the size distribution of spherulites, and the content and distribution of short side chains.

PEG polymers are available in a wide range of molecular weights, ranging from 200 to several millions and with different commercial names. However, the most frequently fraction used as carriers for the manufacture of the so-called 'solid dispersions' range from 1500 to 20000 [3–6]. The preparation of solid dispersions is a technique for enhance the dissolution rate of poorly water soluble drugs by dispersing the drug in a carrier or matrix [7, 8]. The improvement in drug dissolution rate was dependent, for the same drug-carrier ratio, on the elaboration conditions. There are three typical methods for the preparation of solid dispersions: melting (fusion), solvent, or combined melting–solvent methods. The fusion method is the most commonly used to preparing solid dispersions, where a mixture of drug and polymer are directly heated to form a 'co-melt' and subsequently cooled, for instance using an ice bath. Consequently, the thermal history of samples may determine the solid structures, and thus will strongly influence the dissolution rate [9], being not often considered in spite of its importance [4–6]. For this reason, it is necessary to know deeply the thermal behavior of these kind of polymers used as vehicles to reach the best processing conditions of solid dispersions. In the same sense, literature reports regarding the effect of heat treatment and the melting behavior of PEG is scarce [10].

The present work is a contribution to study the effect of the molecular weight and different thermal treatments of a set of several PEG of different molecular weight (1500–200000) analysed using DSC and HSM techniques. The results show here will be useful to know the thermal behavior of commercial samples and the influence of different cooling conditions and ageing, regarding further pharmaceutical processing of solid dispersions.

Experimental

Materials

Flakes of several PEG samples with nominal molecular weights 1500, 4000 and 6000 were supplied by Acofar (Barcelona, Spain). PEG samples ranging from 15000 to 200000 were provided from Serva Laboratories (Barcelona, Catalonia, Spain) and used without further purification. The nominal molecular weight values of this set of PEG samples were accurately garanteed by the suppliers.

Preparation of PEG samples

PEG samples obtained by grinding using a knife-mill were exactly weighted (10±0.1 mg) and placed into flat bottomed aluminum pans of 45 μl. Samples were heated from 303 to 373 K at a heating rate of 10 deg·min^{-1}. The samples were soaked isothermically at 373 K during 10 minutes. Identical thermal treatment was applied to all specimens in order to eliminate the thermal history caused by processing and storage conditions. After this treatment, the samples were inmediately cooled by quenching at different conditions: flash cooled into an ice bath and by immersion in liquid nitrogen, and cooled at room temperature.

Techniques

Differential scanning calorimetry (DSC)

Samples for DSC runs were prepared as described above and heated from 298 to 363 K in air on a Mettler equipment (model FP85), at heating rate of 10 deg·min^{-1}. Melting enthalpies were determined following calibration with high-purity indium supplied by Mettler after integration of the areas under the melting DSC endotherms and using the software supplied with this equipment.

Hot stage microscopy (HSM)

Approximately 0.1 mg of each sample was placed on glass slides with cover-glass and heated at a rate of 5 deg·min^{-1}. Different observations were made during heating using a hot stage optical microscope (Mettler model FP82 HT and Olympus BH-2 microscope). Thus, the temperature at which melting started (thaw point) and the temperature at which complete melting was affected (melting point), were determined by visual observation. These two temperatures were used to define the melting point range of different samples. Runs were made in triplicate and selected micrographs will be shown.

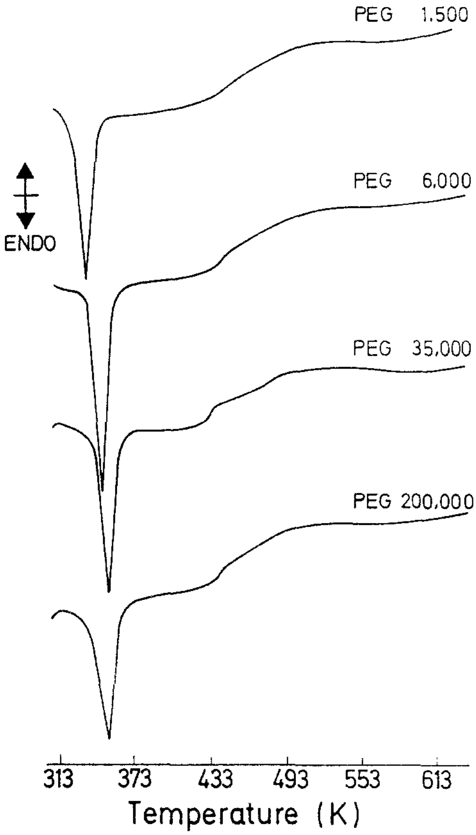

Fig. 1 Representative DSC curves of selected PEG samples with different molecular weight

Results and discussion

Differential scanning calorimetry

Thermal study of untreated PEG samples

Figure 1 displays representative DSC curves of PEG samples with different molecular weights ranging from 1500 to 200000 obtained at a heating rate of 10 deg·min^{-1}. All the DSC curves exhibit a single endothermic peak associated with the melting of the polymer. Their main thermal features from DSC measurements are included in Table 1. The melting points showed an increase with molecular weight in the range 1500 to 20000, after which the values remain practically constant. The peaks start at 313–338 K and finish around 373 K

Table 1 Thermal data of PEG samples

PEG	T_e /K	T_P /K	ΔH/J·g^{-1}	ΔH/kJ·mol^{-1}
1 500	321.5	332.5	–262	–393
4 000	332.0	341.5	–281	–1 124
6 000	333.8	346.8	–291	–1 146
15 000	335.2	347.3	–275	–4 125
20 000	336.7	348.1	–273	–5 460
35 000	335.6	347.0	–263	–9 205
40 000	335.2	347.2	–275	–11 000
100 000	333.2	346.1	–271	–27 100
200 000	330.7	80.5	–250	–50 000

T_e : extrapolated onset temperature; T_P: bottom peak temperature; ΔH: melting enthalpy

with bottom peak temperatures ranging from 333.6 to 356.1 K. All the samples show very similar values of melting enthalpies when the heats of fusion are expressed in J·g^{-1}. However, it is clear that melting enthalpies increase with the molecular weight when they are expressed in kJ·mol^{-1}, as will be shown below.

Figure 2 shows a plot of extrapolated onset temperature (T_e) and peak temperature (T_p) values, obtained from DSC curves, as a function of molecular weight. The melting points show an increase with molecular weight between PEG 1500 and PEG 20000, after which the temperature of melting determined as T_p, does not rise substantially or slightly decreases as determined by the T_e. The melting points here observed are similar to values reported by other authors [10]. It has been suggested that this kind of polymers exhibit a melting range which is dependent on the sample source and preparation conditions, rather than a specific melting point.

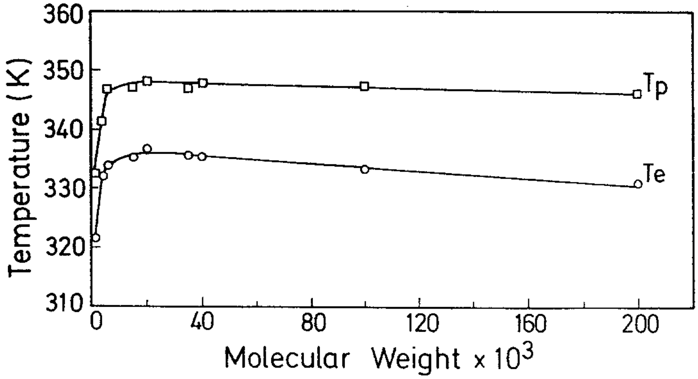

Fig. 2 Plot of melting points, determined as peak (T_p) or extrapolated onset (T_e) temperatures, as a function of PEG molecular weight

The values of melting enthalpies in J·g^{-1} showed a trend to increase as increasing molecular weight (Fig. 3a), with a maximum at PEG 6000, decreasing continuously up to PEG 35000, which shows a value similar to PEG 1500. Other relative maximum is observed at the point of PEG 40000, followed by a decrease and reaching a value at PEG 20000, rather lower than 1500. These results showed the difficulty to obtain relationships between melting enthalpies in J·g^{-1} and PEG molecular weight, in accordance with a previous report [10]. Surprisingly, the results presented in Fig. 3b, have shown a linear relationship between PEG molecular weight and enthalpy data when they are expressed on a molar basis in kJ·mol^{-1}.

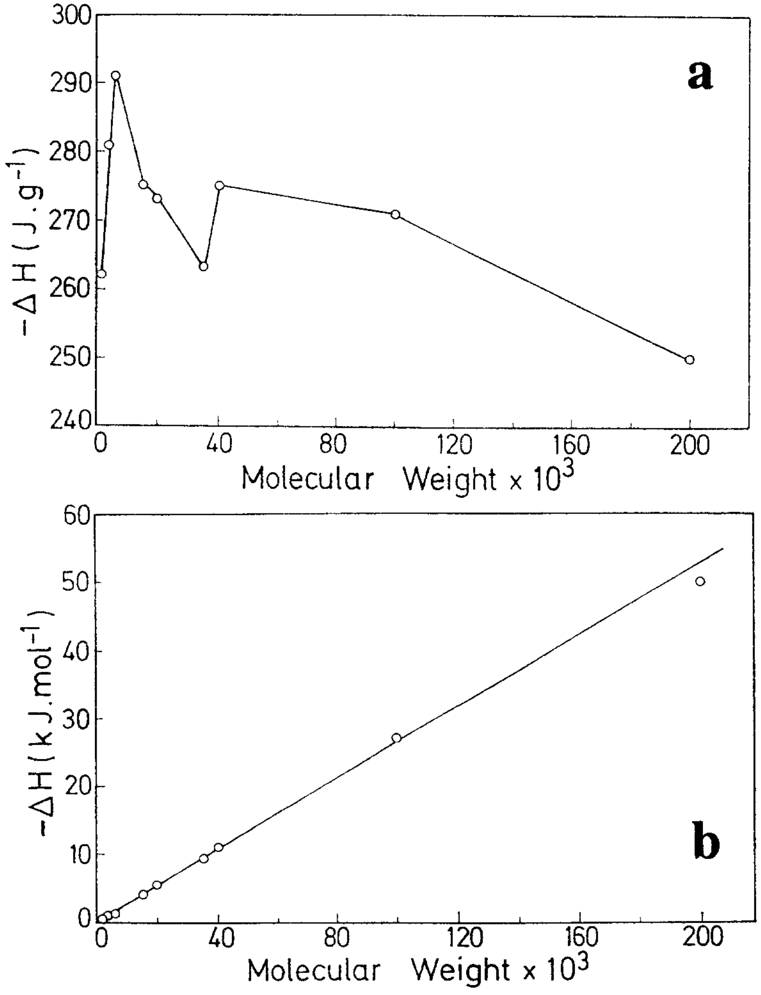

Fig. 3 Plot of melting enthalpies (in J·g^{-1} Fig. 3a; in kJ·mol^{-1} Fig. 3b), as a function of PEG molecular weight

Thermal study of heat treated PEG samples: Influence of cooling rate

Figures 4–7 show the DSC curves of PEG 1500, 4000, 6000 and 15000 after different cooling conditions on solidification of melted samples. In general, it can be observed that the cooling rate seems to determine the shape of the DSC curves obtained. The formation of a shoulder is an evidence of the presence of more than one crystal form within the sample. These results can be explained on the basis of the crystal structure proposed for these polymers. In short, PEG with a molecular weight lower than 4000 always exists as extended chain crystals. In the range of molecular weight 4000–6000 both folded and extended types are found, as pointed out in the introduction. Above this molecular weight range, only folded chain crystals are present in the polymer as a whole [9].

It is clear for the PEG formed by only a type of chain, i.e., PEG with average molecular weight 1500 and 15000, (Figs 4 and 7), that the cooling conditions did not modify apparently the shape of the corresponding DSC curve. For this two PEG samples, the crystal structure remains unaltered after cooling. However, for PEG 4000 and 6000, in which exist evidences of the presence of two types of chains, the shape of the thermogram is influenced by the cooling rate.

For the polymer PEG 4000, all the treatments provide an additional endothermic peak at temperatures below to the melting point detected into the commercial samples. This new endothermic effect must correspond to the folded chains, according to the above exposed, which, in fact, melt at slightly lower temperature seeming less thermodynamically stable than extended chains. The intensity of this endothermal effect depends of two main factors: the cooling rate and the molecular weight of the polymer. Further relevant experiments were performed in this sense. Thus, samples of PEG 4000 cooled at room temperature and studied by DSC, show one endothermal peak centered at 334.5 K, associated to the folded chain, and a second peak at 338.7 K, corresponding to the extended chain (Fig. 5). When the samples were quenched in an ice bath or by immersion in liquid nitrogen, the additional endothermal peak after DSC runs, appeared less accused, being the peak temperatures 333.7 and 333.1 K, respectively. These results are interpreted assuming a diminution in the proportion of folded chains formed after this thermal treatment. However, samples of PEG 6000 solidified from the melt under strictly the same conditions (Fig. 6), only showed an endothermal shoulder associated to the principal one for the samples cooled at room temperature. This result indicates reasonably that the fast cooling treatment yields only one type of polymer chain.

Table 2 summarizes all the data of melting points and heats of fusion for the different samples examined in the present work. From these data, it is deduced that the cooling rate did not modify significantly the melting points of the studied samples, but produces a slight diminution on the melting enthalpy values.

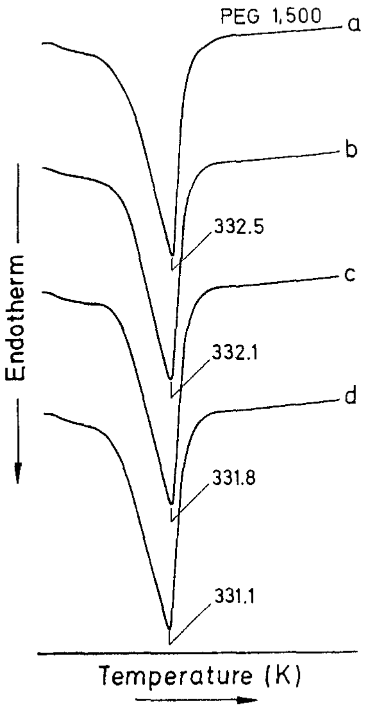

Fig. 4 DSC curves of PEG 1500: (a) original as received sample; (b) slowly cooled at room temperature; (c) flash cooled using an ice bath; (d) flash cooled using liquid nitrogen

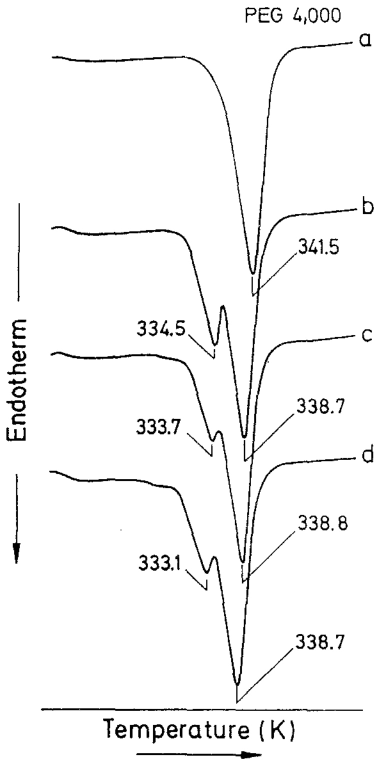

Fig. 5 DSC curves of PEG 4000: (a) original as received sample; (b) slowly cooled at room temperature; (c) flash cooled using an ice bath; (d) flash cooled using liquid nitrogen

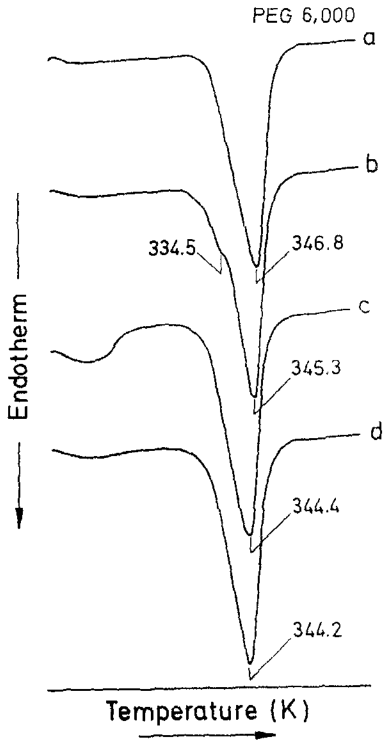

Fig. 6 DSC curves of PEG 6000: (a) original as received sample; (b) slowly cooled at room temperature; (c) flash cooled using an ice bath; (d) flash cooled using liquid nitrogen

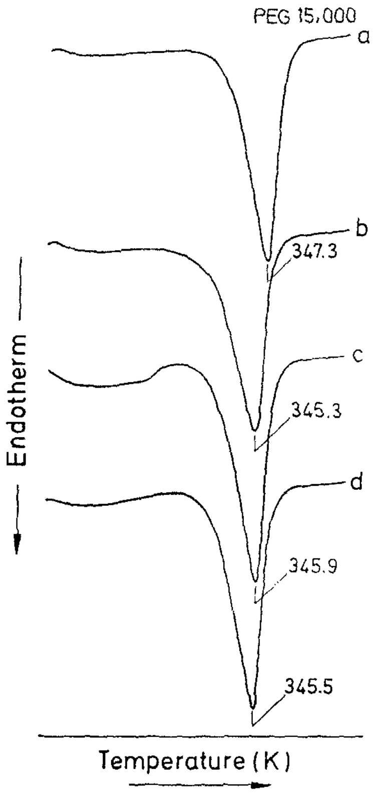

Fig. 7 DSC curves of PEG 15000: (a) original as received sample; (b) slowly cooled at room temperature; (c) flash cooled using an ice bath; (d) flash cooled using liquid nitrogen

This fact can be explained on the basis of the cooling process, which provides a rapid solidification, with the consequent decrease in the crystallinity. From these data, an estimation of folded and extended chain percentages has been carried out on the basis of splitted DSC endothermal peaks. The results are included in Table 2, showing that in PEG 4000 and 6000 these two chain types are present.

Table 2 Thermal data of PEG samples at different cooling conditions

		New *E.E.*		Original *E.E.*			
PEG	Cooling	T_P/K	ΔH/J·g^{-1}	T_P/K	ΔH/J·g^{-1}	% *F. C.*	% *E. C.*
1 500	–	–	–	332.5	–217	–	100
	R. T.	–	–	332.1	–207	–	100
	I. B.	–	–	331.8	–204	–	100
	N_2 liq.	–	–	331.1	–207	–	100
4 000	–	–	–	341.5	–228	–	100
	R. T.	334.5	–66	338.7	–140	32	68
	I. B.	333.7	–52	338.8	–147	26	74
	N_2 liq.	333.1	–59	338.7	–151	28	72
6 000	–	–	–	346.8	–223	100	–
	R. T.	334.5	–31	345.3	–175	15	85
	I. B.	–	–	344.4	–211	100	–
	N_2 liq.	–	–	344.2	–215	100	–
15 000	–	–	–	347.3	–213	100	–
	R. T.	–	–	345.3	–204	100	–
	I. B.	–	–	345.9	–204	100	–
	N_2 liq.	–	–	345.5	–201	100	–

E. E.: endothermic effect; T_p : bottom peak temperature; ΔH: melting enthalpy; *F. C.*: folded chain; *E. C.*: extended chain; *R. T.*: room temperature; *I. B.*: ice bath

Influence of time of storage or ageing on thermal behavior

The complete melting behavior of the slow cooled samples of PEG 4000 and 6000 are showed in Figs 8 and 9, respectively. The results display that the new endothermic effect, caused by the cooling, seems reversible as a function of time of storage. In fact, the folded chains which form PEG 4000 and 6000 are metastable. Thus, PEG 4000 melted and cooled at room temperature after ageing produces a progressive change on the shape of the DSC curves up to a similar situation to the original (Fig. 8). It can be seen that the splitted endothermal effect is reversible to a single endothermal effect after 1 month of ageing stored

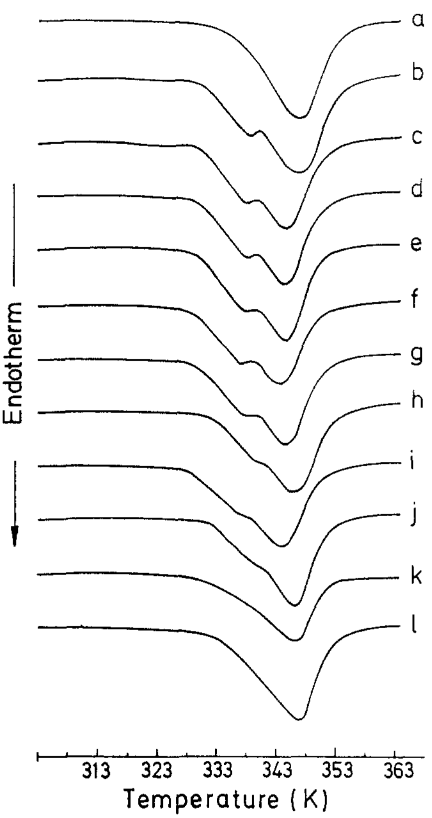

Fig. 8 Effect of ageing on DSC curves of samples of PEG 4000: (a) original as received sample; melted samples at 363 K, solidified at room temperature, and after ageing for: (b) 10 min, (c) 30 min, (d) 60 min, (e) 180 min, (f) 720 min, (g) 1 day, (h) 3 days, (i) 5 days, (j) 7 days, (k) 1 month, and (l) 2 months

at room temperature. This is an effect of ageing on melting behavior: the peak on DSC curves after ageing for 10 min changed progressively to a smaller inflection on the low-temperature side of the melting endotherm after ageing at room temperature for 7 days. This is newly an evidence that the folded chains are thermodynamically less stable in comparison with the extended ones and the thermal evolution after ageing follows that trend.

Finally, Fig. 9 shows that PEG 6000 samples treated under the same conditions after 2 months of ageing still exhibited a shoulder on the main DSC endothermal effect. This is associated to a slower transformation of the polymer chains as compared with the results obtained for the polymer PEG 4000.

Hot stage microscopy

Although all the PEG samples of different molecular weights were studied by HSM, the most representative results for PEG 4000 will be only briefly pre-

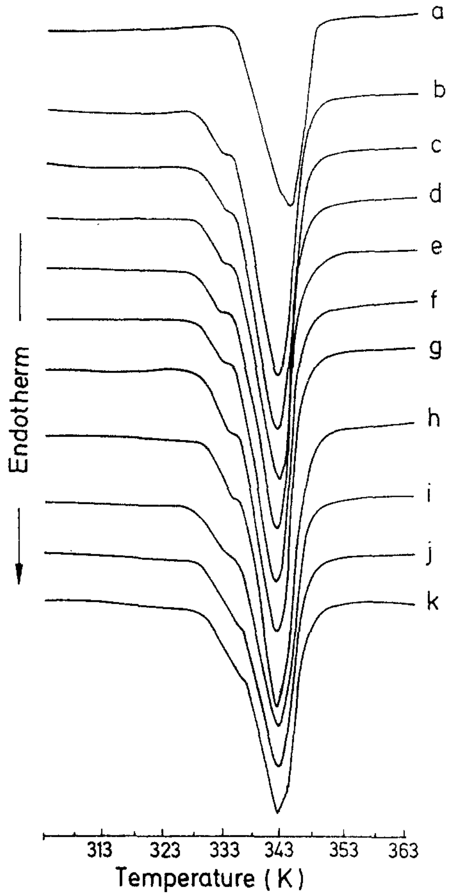

Fig. 9 Effect of ageing on DSC curves of samples of PEG 6000: (a) original as received sample; melted samples at 363 K, solidified at room temperature, and after ageing for: (b) 10 min, (c) 30 min, (d) 60 min, (e) 180 min, (f) 720 min, (g) 1 day, (h) 3 days, (i) 5 days, (j) 1 month, and (k) 2 months

sented in this section to illustrate their thermal features. The general behavior of other PEG samples with lower (1500) and higher (15000) molecular weights was found similar after HSM study.

Figure 10 shows a micrograph corresponding to original (as received) PEG 4000 particles. It is observed its crystalline nature, being confirmed by X-ray diffraction (data not shown). After heating at 5 deg·min^{-1}, the polymer starts to melt at 329 K and small and large vesicles are formed (Fig. 11). Further heating at higher temperatures produces the progressive darkening of these vesicles. This fact is associated to the degradation of the polymer after heating at temperatures upper 473 K (Fig. 12). Finally, at 490 K the melted liquid appeared almost dark, indicating a larger degradation process and subsequent polymer pyrolysis.

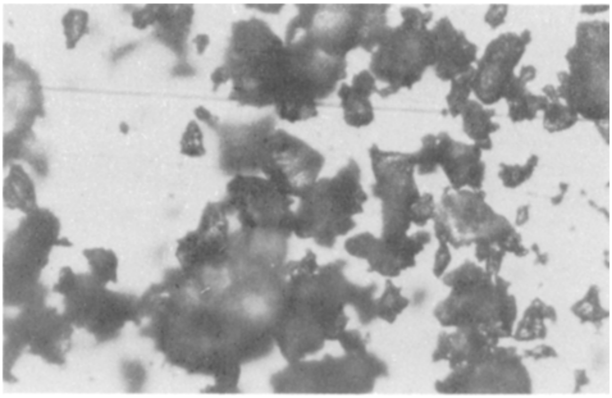

Fig. 10 HSM micrographs of original (as received) PEG 4000 (×400)

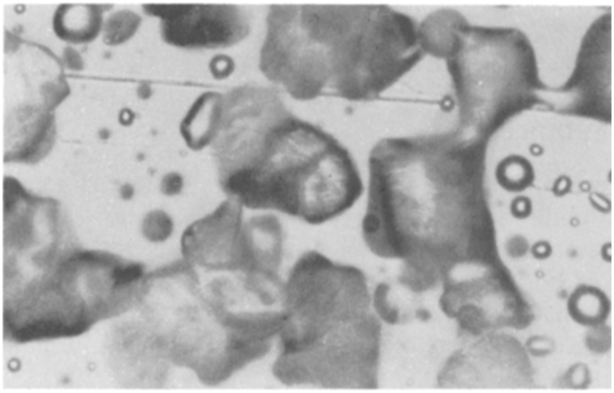

Fig. 11 HSM micrographs PEG 4000, after heating at 329 K (×400). Beginning the melting

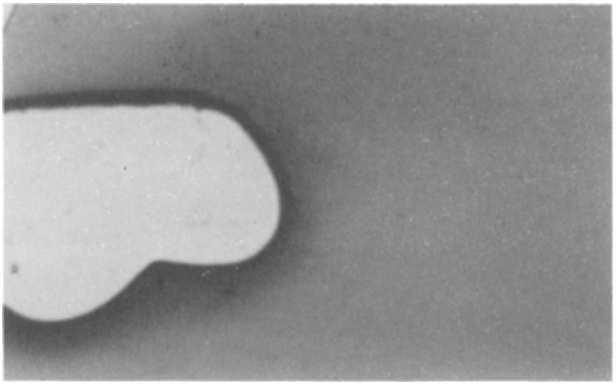

Fig. 12 HSM micrographs of PEG 4000, after heating at 473 K (×400). Beginning of thermal degradation

When PEG 4000 is melted at temperatures below degradation and this is fast cooled, the crystallization of the polymer is nicely observed by HSM as spherulites (Fig. 13), showing their typical radial estriations.

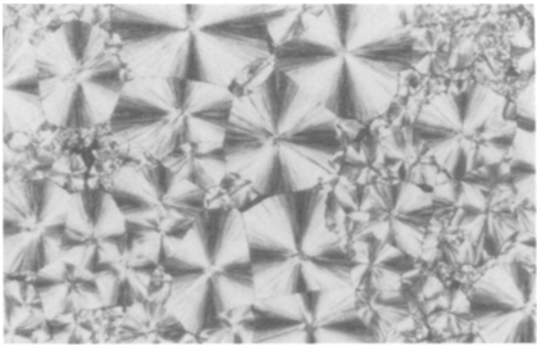

Fig. 13 HSM micrographs of original (as received) PEG 4000, after heating at 363 K and solidified at room temperature (×400)

Concluding remarks

In summary, the results above reported on thermal characterization of PEG samples with a wide range of molecular weights, (1500–200000), have shown that this parameter is not the only factor which determines the degree of chain folding. Other additional factors, such as thermal history of the original (as received) material, particularly the cooling rate from the melting state and time of storage or ageing of solid samples, have further a strong influence on the thermal behaviour studied by DSC.

It is specially remarkable when solid dispersions of drugs are processed by cooling under an ice bath using commercial PEG samples with unknown thermal history. Consequently, it must be take into account to reach reproducible results on drugs dissolution, which will influence their bioavailability.

References

1 F. E. Bailey and J. V. Koleske, Polyethylene oxide, Academic Press, New York 1976.
2 R. C. Allen and L. Mandelkern, J. Polym. Sci.: Polym. Phys. Ed., 20 (1982) 1465.
3 C. Chemtob, S. T. P. Pharma, 1 (1985) 531.
4 P. J. Sánchez-Soto, J. M. Ginés, A. Justo, A. M. Rabasco and J. L. Pérez-Rodríguez, Thermochim. Acta, 158 (1990) 225.
5 J. M. Ginés, P. J. Sánchez-Soto, A. Justo, M. T. Vela and A. M. Rabasco, Drug Dev. Ind. Pharm., 16 (1990) 2283.
6 J. M. Ginés, M. J. Arias, A. M. Rabasco and P. J. Sánchez-Soto, J. Thermal Anal., 40 (1993) 453.
7 J. L. Ford, Pharm. Acta Helv., 61 (1986) 69.
8 J. L. Ford, A. F. Stewart and J. L. Dubois, Int. J. Pharm., 26 (1986) 11.
9 S. M. Chatham, S. T. P. Pharma, 3 (1987) 575.
10 D. Q. M. Craig and J. M. Newton, Int. J. Pharm., 74 (1991) 33.